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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,016	12/20/2001	Anthony J. Celeste	5205BD1	4438

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EXAMINER	
ROMEO, DAVID S	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 12/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/029,016	CELESTE ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-28,35,36,38 and 41-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-28,35,36,38 and 41-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/19/2005 has been entered. Claims 25–28, 35–36, 38 and 41–52 are pending and being examined.

Maintained Formal Matters, Objections And/Or Rejections:

Double Patenting

Claims 25–28, 35–36, 38 and 41–52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6340668, and, if necessary, in view of Wozney (U. S. Patent No. 5,700,911). It is acknowledged that if the claims are allowable Applicants will submit a terminal disclaimer.

Claims 25–28, 38, 43, 44 and 49-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of promoting neuronal cell survival with a polypeptide comprising amino acids 7-108 of SEQ ID NO: 11 or amino acids 1-109 of SEQ ID NO: 11, does not reasonably provide enablement for a method of promoting neuronal cell survival with a polypeptide encoded by a nucleic acid molecule that hybridizes under stringent conditions with the complement of (i) or (ii) or for a method of inducing neurite formation from a neuronal cell or from a neuronal progenitor cell.

The claims are directed to or encompass neurite formation from any neuronal cell or neuronal progenitor cells. Jordan (European Journal of Neuroscience, (1997 Aug) 9 (8) 1699-709) states that:

> BMPs 9 and 11 did not promote the in vitro survival of dopaminergic neurons (page 1703, paragraph bridging left and right columns).
>
> BMP-11 had no effect on BrdU incorporation and astroglial cell maturation, indicating that not all members of the BMP family share effects on proliferation and differentiation of cells in the astrocyte lineage (page 1703, right column, full paragraph 1).
>
> BMPs are distinct from each other with regard to their neurotrophic potentials (page 1705, left column, full paragraph 1).
>
> The BMPs are heterogeneous with regard to their biological effects (paragraph bridging pages 1705-1706).

Wu (Neuron, (2003 Jan 23) 37 (2) 197-207) provides evidence that in the olfactory epithelium (OE), generation of new neurons by neuronal progenitors is inhibited by growth and differentiation factor 11 (GDF11/BMP11) (Abstract).

See also Goldberg (Science. 2002 Jun 7;296(5574):1860-4). The central nervous system (CNS) loses the ability to regenerate early during development. The retina has long served as a simple model system for study of CNS regeneration. Page 1860, Abstract. Neurons in the CNS lose the ability to regenerate their axons early in development (page 1860, paragraph bridging middle and right columns).

The examiner is aware that working examples are not required. However, the lack of working examples is a factor to be considered. The only working examples disclose that BMP-11 promotes survival of PC12 cells under serum-free conditions and that BMP-11 induces neurite formation in PC12 cells. No working examples of neuronal cell survival with any variant

BMP-11 polypeptides is provided. No other working examples of neurite formation in any other type of cell is provided. In view Jordan, Wu, and Goldberg Applicants have failed to establish a nexus between neurite formation in PC12 cells and the full scope of inducing neurite formation from any neuronal cells or from any neuronal progenitor cell. Jordan, Wu, and Goldberg are also evidence that there is a lack of predictability in the art. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of work or testing in the assays than are described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those neuronal cells or neuronal progenitor cells that respond to BMP-11 with neurite formation. It is this additional characterization of that single disclosed, example of neurite formation in PC12 cells that is required in order to obtain the functional data needed to permit one to use the claimed methods that constitutes undue experimentation.

With respect to the hybridization limitation, Applicants argue that hybridization techniques, like antibody production, screening and isolation techniques, were well known in the art at the time the application was filed. Applicants argue that guidance regarding predictable alteration of the sequence is unnecessary because it is not an aspect of the claimed invention. Applicants argue that undue experimentation is not required and that the examiner has not put forward a reasonable basis to doubt the enablement of the claimed invention. Applicant's arguments have been fully considered but they are not persuasive. Applicants disclose a human (SEQ ID NO: 11) and a bovine (SEQ ID NO: 2) BMP11 sequence. Each is identical in the C-terminal, mature, active portion of the molecule. The claims are directed to or encompass a genus of variant BMP-11s encoded by hybridizing molecules. These variant molecules are

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required to promote neuronal cell survival or neurite outgrowth. An antibody is a naturally occurring compound. The present claims are not limited to naturally occurring compounds. In contrast to the repeatable, predictable process of producing an antibody, i.e., immunize with antigen and isolate antibodies that bind antigen, the present specification does not provide a repeatable, predictable process of producing a BMP-11 that meets both the structural and functional limitations of the claims and whose amino acid sequence deviates from what is essentially a single disclosed example of a C-terminal, mature, active portion of a BMP-11 molecule. Applicants' have not shown that hybridization is a repeatable, predictable process of producing variant BMP-11s because Applicants have only obtained BMP-11s that are identical in the C-terminal, mature, active portion of the molecule.

Applicants argue that only routine experimentation would be required to obtain a variant BMP-11 that meets both the structural and functional limitations of the claims. Applicant's arguments have been fully considered but they are not persuasive. The only working examples disclose that BMP-11 promotes survival of PC12 cells under serum-free conditions and that BMP-11 induces neurite formation in PC12 cells. No working examples of neuronal cell survival with any variant BMP-11 polypeptides is provided. No other working examples of neurite formation in any other type of cell is provided. As indicated, Jordan teaches that:

> BMPs are distinct from each other with regard to their neurotrophic potentials (page 1705, left column, full paragraph 1).
>
> The BMPs are heterogeneous with regard to their biological effects (paragraph bridging pages 1705-1706).

Because BMPs are heterogeneous with regard to their biological effects, the listing of percent identity of the C-terminal region of BMP-11 with other TGF-β superfamily members

does not provide the guidance necessary to predictably alter the single disclosed example of BMP-11's mature, C-terminal active portion such that a protein that meets both the structural and functional limitations of the claims is obtained.

Applicants argue that a skilled artisan would not need to predict structure, or develop a structure/function map of any protein to practice the invention. Applicant's arguments have been fully considered but they are not persuasive. The hybridization limitation is a structural limitation of the genus of variant BMP11s. It is the structure that confers the functional properties of the protein. Applicants' have not shown that hybridization is a repeatable, predictable process of producing variant BMP-11s because Applicants have only obtained BMP-11s that are identical in the C-terminal, mature, active portion of the molecule. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of work or testing in the assays than are described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the determination of those amino acid residues in the amino acid sequence of SEQ ID NO: 11 which are required for the structural and functional integrity of that protein. It is this additional characterization of that single disclosed, naturally occurring protein that is required in order to obtain the functional and structural data needed to permit one to produce a "BMP-11" protein which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

New Formal Matters, Objections And/Or Rejections:

Claim Rejections - 35 USC § 112

Claims 38, 43, 44 and 49–52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 38, 43, 44 and 49–52 recite the limitation "neuronal progenitor cell." Support for this limitation cannot be found in the specification as originally filed, which raises the issue of new matter.

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 recites the limitation "neuronal progenitor cell." There is insufficient antecedent basis for this limitation in the claim. The metes and bounds are not clearly set forth.

Claims 43, 44 and 49–52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43, 44 and 49–52 recite "neuronal progenitor cell." There is a lack of antecedent basis for the term "neuronal progenitor cell" in the specification. Although the specification discloses "stem cells" and "neural stem cells," it is unclear if a stem cell, a neural stem cell, or some other type of cell is intended. The metes and bounds are not clearly set forth.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
DECEMBER 11, 2005